

Incidence and Clinical Impact of Dual Nonresponsiveness to Aspirin and Clopidogrel in Patients With Drug-Eluting Stents

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Objectives

This study sought to determine the incidence of aspirin nonresponsiveness in addition to clopidogrel nonresponsiveness and whether this association identifies patients at an increased risk of drug-eluting stent (DES) thrombosis.

Background

Nonresponsiveness to clopidogrel is a predictor of DES thrombosis. No prospective data exist about the possible association of dual nonresponsiveness to clopidogrel and aspirin with DES thrombosis.

Methods

Platelet function was assessed after a loading dose of 600 mg clopidogrel in 746 patients who had successful DES implantation followed by 6-month dual-antiplatelet therapy. Platelet reactivity was assessed by light transmittance aggregometry using adenosine 5'-diphosphate, arachidonic acid, and collagen. The primary end point was definite/probable DES thrombosis at 6 months. The secondary end point was the composite of cardiac mortality and DES thrombosis.

Results

The incidence of dual nonresponsiveness to aspirin and clopidogrel was 6%. Definite/probable DES thrombosis was significantly higher in dual aspirin and clopidogrel nonresponders (11.1%) than in clopidogrel and aspirin responders (2.1%, $p < 0.001$), isolated clopidogrel nonresponders (2.2%, $p < 0.05$), or aspirin nonresponders (2.3%, $p < 0.05$). The incidence of the secondary end point was 4.4% in isolated clopidogrel nonresponders, 2.3% in isolated aspirin nonresponders, and 13.3% in dual aspirin and clopidogrel nonresponders. Dual clopidogrel and aspirin nonresponsiveness was an independent predictor of DES thrombosis (hazard ratio: 3.18, 95% confidence interval: 1.14 to 8.83, $p = 0.027$) and the composite of cardiac mortality and DES thrombosis (hazard ratio: 2.94, 95% confidence interval: 1.16 to 7.41, $p = 0.022$).

Conclusions

Dual nonresponsiveness to aspirin and clopidogrel is a relatively infrequent condition that identifies patients at a very high risk of DES thrombosis or death. (J Am Coll Cardiol 2008;52:734–9) © 2008 by the American College of Cardiology Foundation

Dual antiplatelet treatment with clopidogrel and aspirin is the standard treatment in patients treated with drug-eluting stents (DES) for coronary artery disease for the prevention of DES thrombosis (1–3). Early discontinuation of dual antiplatelet treatment is a strong predictor of DES thrombosis (4–7). However, DES thrombosis can occur also in patients who are compliant with dual antiplatelet treatment, and several retrospective studies and 2 prospective studies have shown that high residual platelet reactivity during antiplatelet treatment is related to the risk of thrombosis

and other adverse events (8–14). The RECLOSE (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-

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Eluting Stent Thrombosis) trial has shown that nonresponsiveness to a loading dose of 600 mg clopidogrel is independently related to the risk of DES thrombosis (14). No prospective data exist about the possible association of dual nonresponsiveness to clopidogrel and aspirin with thrombotic events in patients with DES. This study, based on the RECLOSE trial patient cohort, sought to determine the incidence of aspirin nonresponsiveness in addition to clopidogrel nonresponsiveness and whether this association identifies patients at increased risk of DES thrombosis compared with isolated nonresponsiveness to clopidogrel.

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Methods

Patients. The RECLOSE trial is a prospective study that included 804 consecutive patients who were treated with sirolimus-eluting (Cypher, Cordis Corporation, Miami Lakes, Florida) or paclitaxel-eluting (Taxus, Boston Scientific Corporation, Natick, Massachusetts) stents for coronary artery disease and who were compliant with 6-month dual antiplatelet treatment with aspirin (325 mg daily) and clopidogrel (75 mg daily). Patients with stable coronary artery disease as well as acute coronary syndromes and ST-segment elevation acute myocardial infarction were included irrespective of the coronary anatomy. The only exclusion criteria were: 1) in-hospital death not caused by DES thrombosis; 2) anticipated noncompliance with dual antiplatelet treatment for at least 6 months; and 3) premature discontinuation of clopidogrel or aspirin therapy. The study showed that nonresponsiveness to clopidogrel was associated with a 3-fold increase in DES thrombosis (hazard ratio [HR]: = 3.08, 95% confidence interval [CI]: 1.32 to 7.16, $p = 0.009$) compared with responsiveness. Details of the study have been published elsewhere (14).

Platelet reactivity assessment. By light transmittance aggregometry, we evaluated platelet reactivity testing responsiveness to clopidogrel with adenosine 5'-diphosphate (ADP) and to aspirin with arachidonic acid. Furthermore, we evaluated platelet reactivity using collagen that is an aggregation stimulus not directly involved in the specific pathways of clopidogrel and aspirin. Blood samples anticoagulated with 0.129 mol/l sodium citrate (ratio 9:1) were obtained 12 to 18 h after 600-mg clopidogrel loading. For patients receiving both the loading dose of clopidogrel and a glycoprotein (GP) IIb/IIIa inhibitor in the catheterization laboratory, blood samples were obtained after 6 days, while patients were on the 75-mg maintenance dose of clopidogrel and 325 mg aspirin. Platelet-rich plasma, obtained by centrifuging whole blood for 10 min at 200 g , was stimulated with 10- μ M ADP, 1-mM arachidonic acid, and 2- μ g/ml collagen, and residual aggregation was assessed using a light transmittance aggregometer (APACT4, Helena Laboratories, Milan, Italy). The 100% line was set using platelet-poor plasma, and the 0 baseline was established with platelet-rich plasma (adjusted from $18 \times 10^9/l$ up to $30 \times 10^9/l$). Platelet aggregation (according to the Born method) was evaluated considering the maximal percentage of platelet aggregation in response to stimulus. The coefficient of variation of ADP-, arachidonic acid-, and collagen-platelet aggregation were 6.8%, 5.8%, and 5.6%, respectively. Clopidogrel nonresponsiveness was defined as platelet aggregation by ADP $\geq 70\%$ (14), and aspirin nonresponsiveness as platelet aggregation by arachidonic acid $\geq 20\%$ (15). High residual platelet reactivity by collagen was defined as platelet aggregation above the 90th percentile of aggregation value distribution that resulted in 56%.

End points. The primary end point of the study was definite or probable DES thrombosis during 6-month

follow-up. Definite stent thrombosis was defined as acute coronary syndrome and either angiographic or pathological confirmation of thrombosis. Probable stent thrombosis was defined as sudden or otherwise explained death or nonfatal myocardial infarction in the territory supplied by a stented vessel without angiographic confirmation. The diagnosis of myocardial infarction was based on either the development of new Q waves on 2 or more electrocardiographic leads or an increase of creatine kinase-myocardial band isoenzyme or troponin T $>3\times$ the upper limit of normal. Event time was categorized as acute (within 24 h from stent implantation), subacute (from 1 to 30 days), and late (30 days to 6 months). The secondary end point was the composite of cardiac mortality and definite or probable stent thrombosis. All events were adjudicated by 3 observers (A.M., D.A., G.M.) who were blinded to patient responsiveness to clopidogrel and aspirin and were not involved in the follow-up process.

Follow-up. All patients had scheduled clinical and electrocardiographic examinations at 1, 3, and 6 months. All other possible information derived from hospital readmission or by the referring physician, relatives, or municipality live registries was entered into the database.

Statistical analysis. Discrete data are summarized as frequencies, whereas continuous data are summarized as mean \pm SD. The chi-square test was used for comparison of categorical variables, and the 2-tailed Student t test was used to test differences among continuous variables.

Platelet reactivity test correlations were tested using the 2-tailed Spearman correlation coefficient entering responses to ADP, arachidonic acid, and collagen as continuous variables. The chi-square test was used for comparison among the 4 patient groups, including the post-hoc analysis. The multivariate analysis to evaluate the independent contribution of clinical, angiographic, procedural, and platelet reactivity variables to the primary and secondary end points was performed by a forward stepwise Cox proportional hazards model. Dichotomous platelet reactivity variables according to nonresponsiveness criteria were used (clopidogrel nonresponsiveness, aspirin nonresponsiveness, and the interaction term dual aspirin and clopidogrel nonresponsiveness). The other variables entered into the model were: age (years), male gender, family history of coronary artery disease, smoker, hypertension, hypercholesterolemia, diabetes mellitus, history of myocardial infarction, history of coronary surgery, acute coronary syndrome, acute ST-segment elevation myocardial infarction, left ventricular ejection fraction (%), multivessel disease, bifurcation lesion, thrombus-containing lesion, chronic total occlusion, and stent length (mm). Survival curves were generated using the Kaplan-Meier method, and the difference between the curves was assessed by a log-rank test. A value of $p < 0.05$

Abbreviations and Acronyms

ADP	= adenosine 5'-diphosphate
CI	= confidence interval
DES	= drug-eluting stent(s)
GP	= glycoprotein
HR	= hazard ratio

Table 1 Baseline Characteristics

	Dual Responders (n = 570)	Dual Nonresponders (n = 45)	Isolated Clopidogrel Nonresponders (n = 45)	Isolated Aspirin Nonresponders (n = 86)
Age (yrs)	67 ± 12	73 ± 9*	70 ± 11	72 ± 11
Male gender	435 (76.3)	33 (73.3)	30 (66.7)	65 (75.6)
Current smokers	142 (24.9)	5 (11.1)†	7 (15.6)	16 (18.6)
Arterial hypertension	351 (61.6)	30 (66.7)	29 (64.4)	55 (64.0)
Diabetes mellitus	97 (17.0)	19 (42.2)‡	13 (28.9)†	23 (26.7)†
Hypercholesterolemia	281 (49.3)	19 (42.2)	29 (64.4)†	40 (46.5)
Prior MI	135 (23.7)	12 (26.7)	15 (33.3)	21 (24.4)
Prior PCI	125 (22.0)	9 (20.0)	14 (31.1)	22 (25.6)
Prior CABG	34 (6.0)	4 (8.9)	2 (4.4)	5 (5.8)
Stable angina	186 (32.6)	13 (28.9)	16 (35.6)	34 (39.5)
Unstable angina	206 (36.1)	27 (60.0)‡	22 (48.9)	43 (50.0)†
Acute MI†	174 (30.5)	6 (13.3)†	6 (13.3)†	8 (9.3)‡
Renal failure	60 (10.5)	7 (15.5)	6 (13.3)	10 (11.6)
Multivessel disease	306 (54.1)	33 (73.3)†	27 (60.0)	57 (66.3)†
LVEF (%)	48 ± 11	44 ± 15	46 ± 13	46 ± 13
Multivessel PCI	211 (37.0)	26 (57.8)*	21 (46.7)†	47 (54.7)*
Thrombus-containing lesion	140 (24.6)	5 (11.1)†	3 (6.7)*	10 (11.6)*
Bifurcation lesion	202 (35.4)	16 (35.6)	19 (42.2)	31 (36.0)
Chronic total occlusion	58 (10.1)	9 (20.0)	6 (13.3)	10 (11.6)
Total stent length (mm)	35.6 ± 26.8	51.7 ± 36.2‡	36.2 ± 25.5	44.1 ± 36.9*
Sirolimus-eluting stent	317 (55.6)	23 (51.1)	23 (51.1)	46 (53.5)
Paclitaxel-eluting stent	223 (39.1)	18 (40)	17 (37.8)	30 (34.9)
Both stent types	30 (5.3)	4 (8.9)	5 (11.1)	10 (11.6)
Post-PCI MLD (mm)	2.88 ± 0.45	2.84 ± 0.46	2.81 ± 0.43	2.84 ± 0.50
GP IIb/IIIa inhibitor	258 (45.3)	16 (35.6)	18 (40.0)	30 (34.9)

Data are expressed as n (%) unless otherwise specified. *p < 0.01 versus clopidogrel and aspirin responders; †p < 0.05 versus clopidogrel and aspirin responders; ‡p < 0.001 versus clopidogrel and aspirin responders.

CABG = coronary artery bypass grafting; GP = glycoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MLD = minimum lumen diameter; PCI = percutaneous coronary intervention.

was considered significant. Analyses were performed using the software package SPSS version 8.0 (SPSS Inc., Chicago, Illinois).

Results

Of 804 patients enrolled in the study, complete platelet reactivity data were available for 746 (93%). Clinical and procedural characteristics of the patients investigated according to platelet reactivity are presented in Table 1.

The incidence of dual nonresponsiveness to aspirin and clopidogrel was 6%, whereas isolated nonresponsiveness to

clopidogrel or to aspirin was 6% and 11.5%, respectively. The responses to the 3 stimuli were all correlated: correlation coefficient of ADP and arachidonic acid = 0.536 (p < 0.001), of ADP and collagen = 0.550 (p < 0.001), and of arachidonic acid and collagen = 0.617 (p < 0.001). The follow-up rate was 100%. Table 2 summarizes the clinical outcome at 6 months according to responsiveness to aspirin, clopidogrel, or both drugs.

Overall, definite or probable DES thrombosis occurred in 20 patients (2.7%). Patients with dual nonresponsiveness to clopidogrel and aspirin had the highest incidence of DES

Table 2 6-Month Clinical Outcome

	Dual Responders (n = 570)	Dual Nonresponders (n = 45)	Clopidogrel Nonresponders (n = 45)	Aspirin Nonresponders (n = 86)
Definite/probable stent thrombosis, n (%)	12 (2.1)	5 (11.1)*	1 (2.2)	2 (2.3)†
Definite	6 (1.1)	2 (4.4)	0	1 (1.2)
Probable	6 (1.1)	3 (6.7)‡	1 (2.2)	1 (1.2)
Cardiac death, n (%)	9 (1.6)	4 (8.9)§	2 (4.4)	1 (1.2)†
Composite of cardiac death and stent thrombosis, n (%)	15 (2.6)	6 (13.3)*	2 (4.4)	2 (2.3)†

*p < 0.0001; †p < 0.05 dual clopidogrel and aspirin nonresponders versus aspirin nonresponders; ‡p < 0.05; §p < 0.001 dual clopidogrel and aspirin nonresponders versus clopidogrel and aspirin responders.

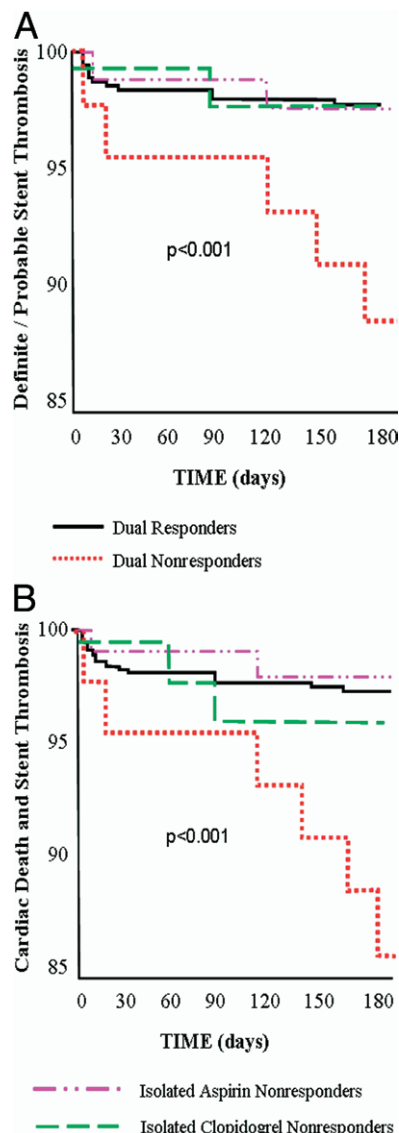


Figure 1 Kaplan-Meier Analysis

Kaplan-Meier analysis of drug-eluting stent thrombosis (A) and the composite of cardiac death and drug-eluting stent thrombosis (B) for dual responders, dual nonresponders, isolated aspirin nonresponders, and isolated clopidogrel nonresponders.

thrombosis (11.1%), whereas responsiveness to both drugs or isolated nonresponsiveness to clopidogrel or aspirin was associated with similar rates of DES thrombosis (2.1%, 2.2%, and 2.3%, respectively; p value among 4 groups = 0.005). Again, the secondary end point rate in patients with dual nonresponsiveness to aspirin and clopidogrel was 3- to 6-fold higher as compared with the other 3 groups: 13.3% in dual nonresponders, 2.6% in dual responders, 4.4% in isolated clopidogrel nonresponders, and 2.3% in isolated aspirin responders (p value among 4 groups = 0.002). Consistent with the results of a previous study (14), nonresponsiveness to clopidogrel with or without nonresponsive-

ness to aspirin ($n = 90$) was associated with an increased risk of DES thrombosis: in the 90 patients, the incidence of DES thrombosis was 6.7% (HR: 3.15, 95% CI: 1.21 to 8.20, $p = 0.019$). Nonresponsiveness to aspirin and dual nonresponsiveness were related to the primary end point (HR: 2.56, 95% CI: 1.02 to 6.40, $p = 0.045$; and HR: 5.31, 95% CI: 1.93 to 14.60, $p = 0.001$, respectively).

The Kaplan-Meier survival curves (Fig. 1) show that the overall risk of DES thrombosis and the composite of cardiac death and DES thrombosis were higher among dual nonresponders compared with the other 3 groups (primary end point: dual nonresponders vs. dual responders, $p < 0.001$; dual nonresponders vs. aspirin nonresponders, $p = 0.036$; dual nonresponders vs. clopidogrel nonresponders, $p = 0.096$; secondary end point: dual nonresponders vs. dual responders, $p < 0.001$; dual nonresponders vs. aspirin nonresponders, $p = 0.011$; dual nonresponders vs. clopidogrel nonresponders, $p = 0.127$).

When platelet function was assessed by collagen, which explores receptors other than those involved in aspirin and clopidogrel pathways, more than one-half of dual nonresponder patients showed an abnormal platelet reactivity (24 of 45 dual nonresponders). In this subgroup of patients, the incidence of the primary end point was higher than in those without residual platelet reactivity (20.8% and 1.8%, respectively; $p < 0.001$). In the other 3 groups, the incidences of abnormal collagen test results were 15.6% (7 patients) in the isolated clopidogrel nonresponder group, 32.6% (28 patients) in the isolated aspirin nonresponder group, and 3.3% (19 patients) in the dual responder group.

At multivariable analysis (Table 3), dual nonresponsiveness to clopidogrel and aspirin was an independent predictor of both DES thrombosis (HR: 3.18, 95% CI: 1.14 to 8.83, $p = 0.027$) and the composite of cardiac mortality and DES thrombosis (HR: 2.94, 95% CI: 1.16 to 7.41, $p = 0.022$). The other variables related to the risk of DES thrombosis and the composite of cardiac death and DES thrombosis were age, total stent length, and left ventricular ejection fraction. If aspirin nonresponsiveness and clopidogrel nonresponsiveness were forced into the multivariable model, the HRs for the primary end point were 1.44 (95% CI: 0.54 to 3.82, $p = 0.463$) and 2.23 (95% CI: 0.85 to 5.82, $p = 0.101$), respectively.

Discussion

This study shows that a high residual platelet reactivity after a loading dose of 600 mg clopidogrel as revealed by 1 or more stimuli is relatively frequent and can be revealed in nearly one-fourth of patients treated with coronary DES. However, dual nonresponsiveness to aspirin and clopidogrel involves only 6% of patients. Patients with dual nonresponsiveness to clopidogrel and aspirin have a very high risk of DES thrombosis during a 6-month follow-up in comparison with dual responders or with isolated clopidogrel or aspirin nonresponders. The present novel findings are not

Table 3

Predictors of DES Thrombosis and the Composite of Cardiac Death and DES Thrombosis

	DES Thrombosis		Cardiac Death and DES Thrombosis	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Dual nonresponsiveness	3.18 (1.14–8.83)	0.027	2.94 (1.17–7.41)	0.022
Total stent length per 1-mm increase	1.01 (1.00–1.02)	0.023	1.01 (1.01–1.02)	0.009
Age per 1-yr increase	1.05 (1.00–1.10)	0.050	1.05 (1.01–1.10)	0.023
LVEF per 1% increase	0.94 (0.91–0.97)	<0.001	0.93 (0.90–0.96)	<0.001

CI = confidence interval; DES = drug-eluting stent; LVEF = left ventricular ejection fraction.

inconsistent with those we previously obtained in the same patient cohort showing that a persistent platelet reactivity to ADP is a predictor of DES thrombosis, because in the previous study, the group of patients with residual platelet reactivity to ADP includes patients with associated residual platelet reactivity to arachidonic acid (14).

One-half of the patients with nonresponsiveness to clopidogrel have associated nonresponsiveness to aspirin. Again, among the dual nonresponders, more than one-half of patients have high residual platelet reactivity by collagen stimulus that explores different pathways other than cyclooxygenase-1 and P2Y12 for the antithrombotic effect of aspirin and clopidogrel. These associations can be explained, at least in part, by the fact that the different pathways involved in platelet reactivity can influence each other at different degrees. Arachidonic acid–induced platelet aggregation is mainly influenced by the inhibition of the thromboxane synthesis, and ADP-induced platelet aggregation is mainly sensitive to the inhibition of P2Y1 and P2Y12 receptors (16–18). However, evidence exists of the role of the P2Y12 receptor, the target of clopidogrel, as a functional regulator of thromboxane-A2 generation consequent to protein-activated receptor stimulation, whereas ADP-induced and collagen-induced platelet aggregation are affected to some extent by aspirin (19,20). Collagen acts on GP VI and directly activates the receptor function of GP IIb/IIIa to induce a maximal platelet aggregation response (21). Signaling by these receptors causes the secretion of ADP, which also participates in GP IIb/IIIa activation.

We did not use tests related to the specific pathways of thromboxane generation and ADP signaling in platelets, and as a consequence, the underlying mechanisms of aspirin, clopidogrel, or dual nonresponsiveness remain unclear. However, it seems likely that an abnormal response to 2 or 3 different platelet aggregation stimuli after a clopidogrel loading dose of 600 mg could define a primary abnormal platelet function as a main cause of thrombotic events, and that “aggressive blood” makes the patient a “vulnerable patient.”

Clinically it seems relevant that a single platelet aggregation assessment after clopidogrel loading may provide a definite risk profile for DES thrombosis despite the lack of standardization in definition of clopidogrel and aspirin resistance (22), and the fact that in vitro platelet responsiveness may be quite variable because of the influence of

several factors, such as inadequate generation of the active drug metabolite of clopidogrel or differences in the rate of intestinal absorption of antiplatelet drugs (18,21,23). Again, in this study the majority of patients had an acute coronary syndrome or ST-segment elevation acute myocardial infarction, which are conditions associated with higher baseline platelet reactivity compared with stable coronary artery disease (24,25), and it is surprising that a single platelet reactivity assessment in the acute phase of coronary artery disease maintains a high predictive value for subacute or late DES thrombosis when most patients are stable and the evidence of the acuity of coronary disease has disappeared. **Study limitations.** The deferred blood sample collection in patients who received GP IIb/IIIa inhibitors could have the potential for a confounding effect on the assessment of residual platelet reactivity to the collagen stimulus. However, this confounding effect is unlikely, considering the delay from the GP IIb/IIIa inhibitor administration and the assessment of platelet reactivity.

The analysis according to platelet responsiveness to both aspirin and clopidogrel decreases the statistical power of the sample size used in the RECLOSE trial, which was sufficiently powered for the responsiveness to clopidogrel with or without nonresponsiveness to aspirin. However, the concentration of DES thrombosis and mortality in the dual nonresponders patient group is impressive, whereas no other data from prospective studies on dual aspirin and clopidogrel nonresponsiveness in patients treated with DES are currently available. This limitation highlights the need for a large-scale confirmatory trial; meanwhile, the findings of this study should be considered as hypothesis generating rather than offering a definitive answer.

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